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Guidelines for Carcinogen Risk Assessment

Risk Assessment Forum
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profiles, physicochemical properties, and structure-activity relationship (SAR) analyses in a weight-of-evidence approach (Dearfield et al., 1991; U.S. EPA, 1986b; Waters et al., 1999). Key data for a mutagenic mode of action may be evidence that the carcinogen or a metabolite is DNA-reactive and/or has the ability to bind to DNA. Also, mutagenic carcinogens usually produce positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, and in tests performed *in vivo* which generally are supported by positive tests *in vitro*. Additionally, carcinogens may be identified as operating via a mutagenic mode of action if they have similar properties and SAR to mutagenic carcinogens. Endpoints that provide insight into an agent's ability to alter gene products and gene expression, together with other features of an agent's potential mode of carcinogenic action, are discussed below.

2.3.5.1. *Direct DNA-Reactive Effects*

It is well known that many carcinogens are electrophiles that interact with DNA, resulting in DNA adducts and breakage (referred to in these cancer guidelines as direct DNA effects). Usually during the process of DNA replication, these DNA lesions can be converted into and fixed as mutations and chromosomal alterations that then may initiate and otherwise contribute to the carcinogenic process (Shelby and Zeiger, 1990; Tinwell and Ashby, 1991; IARC, 1999). Thus, studies of mutations and other genetic lesions continue to inform the assessment of potential human cancer hazard and in the understanding of an agent's mode of carcinogenic action.

EPA has published testing guidelines for detecting the ability of an agent to damage DNA and produce mutations and chromosomal alterations (as discussed in Dearfield et al., 1991). Briefly, standard tests for gene mutations in bacteria and mammalian cells *in vitro* and *in vivo* and for structural chromosomal aberrations *in vitro* and *in vivo* are important examples of relevant methods. New molecular approaches, such as mouse mutations and cancer transgenic models, are providing a means to examine mutation at tissue sites where the tumor response is observed (Heddle and Swiger, 1996; Tennant et al., 1999). Additionally, continued improvements in fluorescent-based chromosome staining methods (fluorescent *in situ*